

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number  
**WO 02/41044 A2**

(51) International Patent Classification<sup>7</sup>: G02B 1/04, C08L 43/04, 83/04, A61L 12/00

(21) International Application Number: PCT/US01/48474

(22) International Filing Date: 29 October 2001 (29.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
09/713,464 15 November 2000 (15.11.2000) US

(71) Applicant: JOHNSON & JOHNSON VISION CARE, INC. [US/US]; 7500 Centurian Parkway, Suite 100, Jacksonville, FL 32256 (US).

(72) Inventors: VANDERLAAN, Douglas, G.; 8114 Parkridge Cir. S., Jacksonville, FL 32211 (US). GALAS, Stephen, L.; 4617 Cape Elizabeth Ct. E., Jacksonville, FL 32277 (US).

(74) Agents: JOHNSON, Philip, S. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

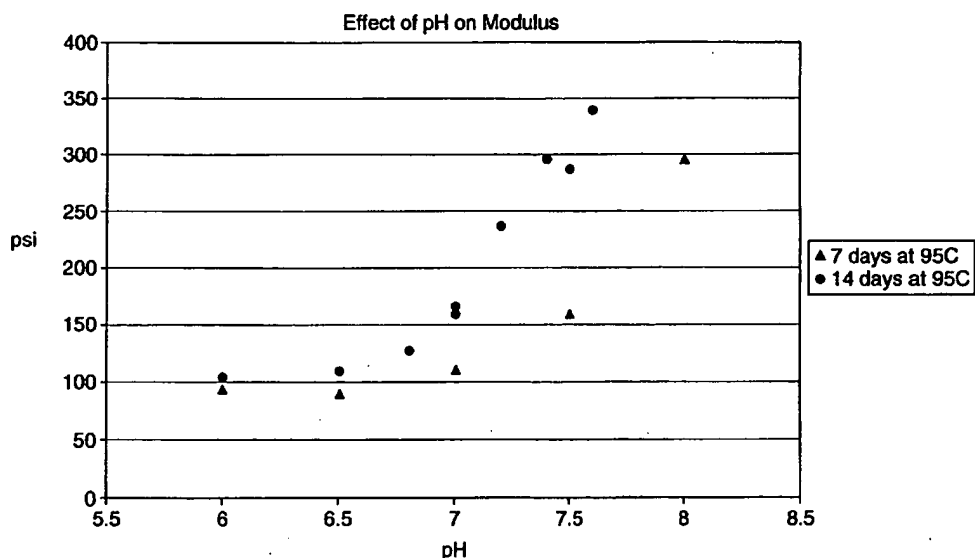
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS OF STABILIZING SILICONE HYDROGELS AGAINST HYDROLYTIC DEGRADATION



(57) Abstract: A method of increasing the shelf life of silicone hydrogels stored in aqueous solutions.

WO 02/41044 A2

## METHODS OF STABILIZING SILICONE HYDROGELS AGAINST HYDROLYTIC DEGRADATION

### FIELD OF THE INVENTION

5        This invention relates to methods of stabilizing silicone hydrogels against hydrolytic degradation.

### BACKGROUND OF THE INVENTION

      Contact lenses have been used commercially to improve vision since at least the 1950s. The first contact lenses were made of hard materials and as  
10    such were somewhat uncomfortable to users. Modern lenses have been developed that are made of softer materials, typically hydrogels and particularly silicone hydrogels. Hydrogels are water-swollen polymer networks that have high oxygen permeability and provide good comfort to lens users. These materials have enabled many more patients to wear lenses due to their  
15    increased comfort. Despite the advantages of these lenses to patients, the same lenses present unique problems to the manufactures of those lenses

      Contact lenses, like other medical devices, are stored in aqueous solutions. The mechanical properties of silicone hydrogel contact lenses degrade over time when lenses are stored at ambient or elevated temperature  
20    in aqueous solutions. This degradation, shortens the shelf life of a silicone hydrogel and can be quantified by measuring the increase in tensile modulus. Therefore, there is a need to find a method of increasing the stability of silicone hydrogel contact lenses in aqueous solutions. It is this need that this invention fills.

### 25        BRIEF DESCRIPTION OF THE DRAWINGS

      Figure 1 Graph illustrating the effect of pH on tensile modulus.

### DETAILED DESCRIPTION OF THE INVENTION

      This invention includes a method of stabilizing a silicone hydrogel article against hydrolytic degradation comprising, consisting essentially of, or  
30    consisting of, storing said silicone hydrogel in an ozone-free, aqueous solution having a pH of from about 5.0 to less than about 7.2, and a viscosity of less than about 10 centipoise, wherein if the aqueous solution contains a

poloxamine or poloxamer surfactant, the surfactant is present in an amount less than about 0.005 weight percent.

As used herein, the term "silicone hydrogel article" refers polymers that absorb water and are made of at least one silicone monomer, co-polymerized with a hydrophilic monomer. Examples of typical silicone monomers include but are not limited to 3-methacryloxypropyl tris(trimethylsiloxy)silane (TRIS), and monomethacryloxypropyl terminated polydimethylsiloxane (mPDMS), m vinyl[3-[3,3,3-trimethyl-1,1bis(trimethylsiloxy)disiloxanyl]propyl]carbamate, 3-methacryloxypropylbis (trimethylsiloxy)methyl silane, and methacryloxypropylpentamethyl disiloxane. Additional monomers are described in U.S. Pat. Nos. 4,711,943; 3,808,178; 4,139,513; 5,070,215; 5,710,302; 5,714,557; 5,908,906; 4,136,250; 4,153,641; 4,740,533; 5,034,461; 5,070,215; 5,260,000; 5,310,779; and 5,358,995 which are hereby incorporated by reference for the silicone monomers contained therein. Examples of hydrophilic monomers include but are not limited to unsaturated carboxylic acids, such as methacrylic and acrylic acids; acrylic substituted alcohols, such as 2-hydroxyethylmethacrylate and 2-hydroxyethylacrylate; vinyl lactams, such as N-vinyl pyrrolidone; and acrylamides, such as methacrylamide and N,N-dimethylacrylamide. Still further examples include  $\beta$ -alanine-N-vinyl ester, the hydrophilic vinyl carbonate or vinyl carbamate monomers disclosed in U.S. Pat. No. 5,070,215, and the hydrophilic oxazolone monomers disclosed in U.S. Pat. No. 4,910,277. U.S. Pat Nos. 5,070,215, and 4,910,277 are hereby incorporated by reference with respect to the silicone monomers contained therein.

This invention can be used in conjunction with all types of silicone hydrogels articles. The problem of modulus increase associated with hydrolytic degradation may be particularly pronounced when silicone hydrogels contain carboxylic acid-functional monomers. Silicone hydrogels containing those monomers suffer more hydrolytic degradation upon standing than those that do not contain monomers with carboxylic acid functionality.

Silicone hydrogels are used to form a number of medical devices, particularly contact lenses and intraocular lenses. Examples of procedures to

prepare silicone hydrogel contact lenses may be found in U.S. Pat. 5,260,000, U.S. Pat. No. 6,037, 328, U.S. Pat. No. 5,998,498, US Pat. App. No. 09/532,943, a continuation-in-part of US Pat. App. No. 09/532,943 filed on August 30, 2000, U.S. Patent No. 6,087,415, U.S. Pat. No. 5,962,548, and  
5 U.S. Pat No. 6,020,445. This invention is particularly suited for contact lens made from aquafilcon A, balafilcon A and lotrafilcon.

"Ozone-free" solutions are those that do not contain dissolved ozone, other than the ozone that diffuses into the solution from the atmosphere.

"Aqueous solutions" include but are not limited to any water based solution that  
10 is used for the storage or washing of contact lenses. Typical solutions include saline solutions, other buffered solutions, and deionized water. The preferred aqueous solution is a saline solution where the salts contained therein are selected from one or more members of the group consisting of sodium chloride, boric acid, sodium borate, sodium phosphate, sodium  
15 hydrogenphosphate, sodium dihydrogenphosphate, or the corresponding potassium salts of the same. These salts are generally combined to form buffered solutions which include an acid and its conjugate base, so that addition of acids and bases cause only a relatively small change in pH. The buffered solutions may additionally include 2-(N-morpholino)ethanesulfonic acid (MES), NaOH, 2,2-bis(hydroxymethyl)-2,2',2"-nitrilotriethanol, HCl,  
20 n-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid, citric acid, sodium citrate, sodium carbonate, sodium bicarbonate, acetic acid, sodium acetate. The concentration of salt in the aqueous solution is about 0.3 to 3.0 weight percent, preferably about 0.5 to 2.0 percent, more preferably about 0.6 to 1.3  
25 percent. The preferred buffer solutions are borates and phosphates.

The pH of the aqueous solution can be adjusted to a pH of about of about 5.0 to less than about 7.2 by the addition of aqueous HCl or aqueous NaOH. The preferred pH ranges from about 6.0 to about less than 7.2, more preferably from about 6.8 to about 7.2, most preferably from about 6.8 to about  
30 7.1. The viscosity of the aqueous solution is less than about 10 centipoise and preferably less than about 7 centipoise.

Further, the invention includes a hydrolytically stable silicone hydrogel contact lens that is produced by a method comprising, consisting essentially of, or consisting of, storing said silicone hydrogel in an ozone-free, aqueous solution having a pH of from about 5.0 to less than about 7.2, and a viscosity of  
5 less than about 10 centipoise, wherein if the aqueous solution contains a poloxamine or poloxamer surfactant, the surfactant is present in an amount less than about 0.005 weight percent. The terms silicone hydrogel and aqueous solution all have their aforementioned meanings and preferred ranges. "Hydrolytically stable," refers to a lens whose tensile modulus  
10 increases less than the tensile modulus of another lens, made of the same material, that has been stored at a pH of more than about 7.3.

In order to illustrate the invention the following examples are included. These examples do not limit the invention. They are meant only to suggest a method of practicing the invention. Those knowledgeable in contact lenses as  
15 well as other specialties may find other methods of practicing the invention. However, those methods are deemed to be within the scope of this invention.

#### EXAMPLES

The following abbreviations were used in the examples

Lens A = aquafilcon A  
20 Lens B = balafilcon A  
DI= deionized water  
EDTA = ethylenediaminetetraacetic acid  
phosphate-buffered saline, pH  $7.4 \pm 0.2$  = PBS;  
Phosphate-buffered saline with 0.05% Tween 80, pH  $7.4 \pm 0.2$  = TPBS;

25

#### Example 1

##### Measurement of the Mechanical Properties of Lens A at Different pH

Tensile modulus was determined as follows. Twelve lenses were cut into dog-bone shapes and the modulus and elongation to break were  
30 measured using and INSTRON™ Model 1122 tensile tester. The lenses were hydrated, using their original packing solution, immediately prior to undergoing testing. The tensile modulus of the 12 lenses were averaged to obtain the

mean modulus for the set. Lens A had a modulus of  $85.6 \pm 10.3$  psi when tested prior to conditioning. A saline solution was prepared from 8.48 g/l NaCl, 9.26 g/l boric acid, 1.00 g/l sodium borate and 0.10 g/l EDTA in water. The pH of the solution was adjusted to pH's 6.0, 6.5, 7.0, 7.5 and 8.0 by the addition of small amounts of either 50% NaOH aq. or 37% HCl aq. The lenses were placed in each pH solution and the mixture was heated to 95°C in sealed vials. The mechanical properties (tensile modulus) of these lenses were measured after one and two weeks at this temperature. The results are shown in Table 1 and Figure 1.

Table 1

	After 1 week @ 95 °C	After 2 weeks @ 95 °C
pH	Modulus (psi)	Modulus (psi)
6.0	$92.9 \pm 4.0$	$104.7 \pm 6.3$
6.5	$89.1 \pm 3.3$	$108.8 \pm 5.0$
6.8		$126.3 \pm 9.9$
7.0		$164.3 \pm 16$
7.0	$109.9 \pm 14.8$	$157.8 \pm 11.7$
7.2		$236.1 \pm 11.8$
7.4		$295.9 \pm 28.5$
7.5	$158 \pm 17.7$	$286.8 \pm 24.4$
7.6		$338.8 \pm 42.6$
8.0	$294.9 \pm 75.2$	$532 \pm 76$

The numerical value of a lens' modulus is inversely proportional to its hydrolytic stability: the lower modulus number, the more stable the lens. These results show that as the pH of the storage solution is lowered, the mechanical stability of the silicone hydrogel increases.

## Example 2

Measurement of the Mechanical Properties of Lenses B at Different pH

The mechanical properties of Lens B was measured. Lens B has a modulus of 155 (20) psi when tested prior to conditioning. Lenses were placed into saline solution made as in Example 1 at pH's 6.0, 7.0 and 8.0 and heated to 95°C in sealed vials. The mechanical properties of these lenses were measured after one week at this temperature.

Table 2

After 1 week @ 95 °C.	
pH	Modulus (psi)
6.0	544 ± 45
7.0	576 ± 21
8.0	1217 ± 102

## Example 3

Vifilcon (a silicone-free copolymer of 2-hydroxyethyl methacrylate, methacrylic acid, N-vinylpyrrolidone and ethyleneglycol dimethacrylate) soft contact lenses, with an initial modulus of  $73.1 \pm 7.2$  psi, were placed into saline solution made as in Example 1 at pH's 6.0, 7.0 and 8.0 and heated to 95°C in sealed vials. The mechanical properties of these lenses were measured after two weeks at this temperature. The results, in Table 3, show that unlike those of silicone hydrogels, the moduli of non-silicone hydrogels change very little in accelerated aging tests, and in fact may actually decrease slightly at higher pH.

Table 3

After 2 weeks @ 95 °C.	
pH	Modulus (psi)
6.0	75.7 ± 4.6
7.0	68.2 ± 5.9
8.0	64.9 ± 4.4

What is claimed is:

1. A method of stabilizing a silicone hydrogel article against hydrolytic degradation comprising, storing said silicone hydrogel in an ozone-free, aqueous solution having a pH of from about 5.0 to less than about 7.2, and a viscosity of less than about 10 centipoise, wherein if the aqueous solution contains a poloxamine or poloxamer surfactant, the surfactant is present in an amount less than about 0.005 weight percent.
2. The method of claim 1 wherein the aqueous solution is saline solution comprising salts selected from one or more members of the group consisting of sodium chloride, boric acid, sodium borate, sodium phosphate, sodium hydrogenphosphate, sodium dihydrogenphosphate, or the corresponding potassium salts of the same.
3. The method of claim 2 wherein the concentration of salt is about 0.3 to 3.0 weight percent.
4. The method of claim 1 wherein the pH of the aqueous solution is about 6.8 to about 7.2.
5. The method of claim 1 wherein the silicone hydrogel article comprises a contact lens.
6. The method of claim 5 wherein the contact lens comprises aquafilcon A, balafilcon A, or lotrafilcon.
7. The method of claim 1 wherein the viscosity is less than about 7 cps.
8. A silicone hydrogel contact lens that is produced by a method comprising storing said silicone hydrogel in an ozone-free, aqueous solution having a pH of from about 5.0 to less than about 7.2, and a viscosity of less than about 10 centipoise, wherein if the aqueous



solution contains a poloxamine or poloxamer surfactant, the surfactant is present in an amount less than about 0.005 weight percent.

- 5      9.    The contact lens of claim 8 wherein the pH of the aqueous solution is about 6.8 to about 7.1.
10.    The contact lens of claim 8 wherein said contact lens further comprises aquafilcon A, balafilcon A and lotrafilcon.

10

15

20

25

30

1/1

**FIG. 1**

Effect of pH on Modulus

